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The Ritter Reaction of α -Oxo-benzeneacetonitrile with Several Compounds Capable of Forming a Carbonium Ion

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Methylene-*bis*-(α -oxo-benzeneacetamide), *N*-(1-methylcyclohexyl)- α -oxo-benzeneacetamide, *N*-(2-methylcyclohexyl)- α -oxo-benzeneacetamide, *N*-(3-methylcyclohexyl)- α -oxo-benzeneacetamide and *N*-(1-methylcyclopentyl)- α -oxo-benzeneacetamide were synthesized in moderate yields by the Ritter reaction of α -oxo-benzeneacetonitrile with α -trioxymethylene, 1-methyl-1-cyclohexene, 3-methyl-1-cyclohexene, 4-methyl-1-cyclohexene and 1-methyl-1-cyclopentene, respectively.

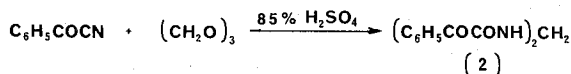
KEY WORDS: The Ritter Reaction/ α -Oxo-benzeneacetonitrile/ α -Trioxymethylene/ Methylene-*bis*-(α -oxo-benzeneacetamide)/ 1-Methyl-1-cyclohexene/ *N*-(1-Methylcyclohexyl)- α -oxo-benzeneacetamide/ 3-Methyl-1-cyclohexene/ *N*-(2-Methylcyclohexyl)- α -oxo-benzeneacetamide/ 4-Methyl-1-cyclohexene/ *N*-(3-Methylcyclohexyl)- α -oxo-benzeneacetamide/ 1-Methyl-1-cyclopentene/ *N*-(1-Methylcyclopentyl)- α -oxo-benzeneacetamide/

The easy applicability of the Ritter reaction to almost all of nitriles, regardless of their classification between aliphatic and aromatic or saturated and unsaturated, is well known from Ritter's original investigation.¹⁾ It is also evident from the several reports that the nitriles having another functional group such as halo,²⁾ hydroxy,³⁾ alkoxy,⁴⁾ amino⁵⁾ or carbalkoxy⁶⁾ can be utilized as a nitrile source in the Ritter reaction. The reaction has further been extended to the employment of such cyanide as hydrocyanic acid,⁷⁾ cyanogen,⁸⁾ cyanogen chloride,⁹⁾ cyanomide,¹⁾ 1-cyanoformamide¹⁰⁾ or dicyandiamide⁸⁾ instead of the above-mentioned nitriles. However, there is no reference concerning the employment of acyl cyanide such as α -oxo-benzeneacetonitrile as the nitrile source except only one patent literature.¹¹⁾ The patent literature claims the formation of *N*-(1,1-dimethylethyl)- α -oxo-benzeneacetamide¹²⁾ (**1**) in 95% yield by the addition of α -oxo-benzeneacetonitrile to *tert*-butyl alcohol in dichloromethane in the presence of concentrated sulfuric acid. The reinvestigation of this reaction under the reaction conditions used by us (see Experimental section) indicated that the yield of **1** is high as 46%. It has also been found that the reaction of α -oxo-benzeneacetonitrile with some primary alcohols¹³⁾ such as butyl and benzyl alcohols under the reaction conditions used by us gives none of the expected *N*-alkyl- α -oxo-benzeneacetamide but only the corresponding benzoates, indicating the occurrence of benzylation of such the alcohols with α -oxo-benzeneacetonitrile under acidic conditions.¹⁴⁾

Next, the Ritter reaction of α -oxo-benzeneacetonitrile with α -trioxymethylene providing methylene-*bis*-(α -oxo-benzeneacetamide) (**2**) was studied. The reaction was conducted by

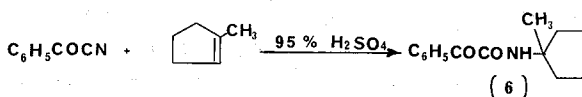
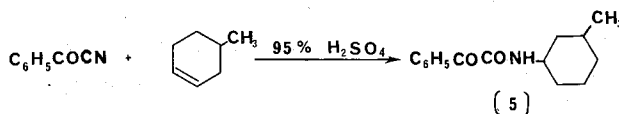
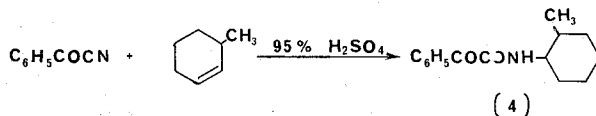
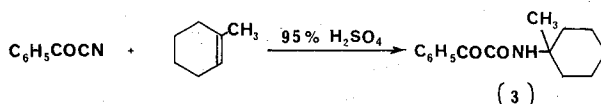
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adding a mixture of α -oxo-benzeneacetonitrile and a slightly excess of α -trioxymethylene into 85% sulfuric acid at low temperature (see Experimental section). The yield of **2** was as high as 38%.



A considerable lowering of the yield has been brought about whenever the reaction conditions were altered; the use of more excess of 85% sulfuric acid, the change of sulfuric acid concentration into 95%, increasing the quantity of α -trioxymethylene used and the alteration of reaction temperature were all bad to this reaction.

The extension of the Ritter reaction with *tert*-butyl alcohol initially mentioned to the appropriate cycloalkenes has enabled us to synthesize some *N*-cycloalkyl- α -oxo-benzeneacetamides (**3**, **4**, **5** and **6**). The cases in which some cycloalkenes having a methyl group were used in the reaction are documented in Table I.

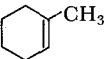
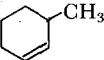
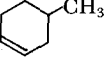
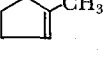


However, their parent compounds, cyclopentene and cyclohexene, as well as cycloheptene gave none of the expected Ritter product but only the corresponding cycloalkyl acetates. On the basis of detailed knowledge concerning the mechanism of the Ritter reaction it is easily understandable that the presence of a methyl group facilitate the occurrence of expected reaction.

When α -methylstyrene was used instead of the cycloalkene, two compounds, 2,4-diphenyl-4-methyl-1-pentene¹⁵⁾ (**7**) and -2-pentene¹⁵⁾ (**8**) (3:2) were formed in relatively low yields. The same result has also been obtained in such case that α -oxo-benzeneacetonitrile was gone out of use. The reaction seems to involve only the dimerization of α -methylstyrene,¹⁵⁾ probably because the initially formed carbonium ion from α -methylstyrene is too weak to attack the coexistent α -oxo-benzeneacetonitrile molecule.

Ritter Reaction of α -Oxo-benzeneacetonitrile

 Table I. The Ritter Addition of α -Oxo-benzeneacetonitrile to Some Compounds Capable of Forming a Carbonium Ion

Entry	Carbonium ion source	Product	Yield (%)
1	$(\text{CH}_3)_3\text{COH}$	$\text{C}_6\text{H}_5\text{COCONHC}(\text{CH}_3)_3$ (1)	46
2	$(\text{CH}_2\text{O})_3$	2	38 ^{a)}
3		3	56
4		4 ^{b)}	37
5		5 ^{b)}	36
6		6	34
7	$\text{C}_6\text{H}_5\text{C}(\text{CH}_3)=\text{CH}_2$	$\left\{ \begin{array}{l} \text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{CH}_2\overset{\text{CH}_2}{\underset{\text{H}}{\text{C}}}\text{C}_6\text{H}_5 \\ \text{(7)} \\ + \\ \text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{CH}=\text{C}(\text{CH}_3)\text{C}_6\text{H}_5 \\ \text{(8)} \\ \text{(3:2)} \end{array} \right\}$	30 ^{c)}

a) The yield of **2** was same even if paraformaldehyde was used instead of α -trioxymethylene.

b) It is reasonable to assume that **4** and **5** possess such structures as formulated in this text.

c) Total yield of **7** and **8**.

Table II. Physical Properties and Analytical Data of the New Compounds

Compound	Mp ($^{\circ}\text{C}$) or bp ($^{\circ}\text{C}/\text{mmHg}$)	$^1\text{H-NMR}$ (δ , in CDCl_3)	Found (Calcd) (%)		
			C	H	N
2	157–159.5 [$\text{C}_2\text{H}_5\text{OH}/\text{Hexane}$ (1:1)]	4.97 (dd, 2H), 7.3–7.7 and 8.0–8.5 (m and m, 12H)	66.08 (65.80)	4.62 (4.55)	8.95 (9.03)
3	183 (Petroleum ether)	1.1–1.9 (m, 10H), 1.30 (s, 3H), 7.2–7.6 and 7.9–8.3 (m and m, 6H)	73.52 (73.44)	7.81 (7.81)	5.80 (5.71)
4	150–152/0.4	0.8–1.0 (m, 3H), 1.1–1.8 and 1.8–2.3 (m and m, 9H), 4.9–5.3 (m, 1H), 7.2–7.7 and 8.2–8.4 (m and m, 6H)	73.48 (73.44)	7.77 (7.81)	5.83 (5.71)
5	72–73 (Petroleum ether)	0.87 (d, 3H), 1.1–1.9 (m, 8H), 1.9–2.2 (m, 1H), 4.8–5.1 (m, 1H), 7.2–7.9 and 7.9–8.3 (m and m, 6H)	73.45 (73.44)	7.89 (7.81)	5.69 (5.71)
6	50–52 (Petroleum ether)	1.50 (s, 3H), 1.5–2.4 (m, 8H), 7.17 (bs, 1H), 7.4–7.8 and 8.2–8.5 (m and m, 5H)	72.47 (72.70)	7.38 (7.41)	6.20 (6.05)

EXPERIMENTAL

The Ritter Addition of α -Oxo-benzeneacetonitrile to *tert*-Butyl Alcohol or Either One of the Alkenes (Entries 1 and 3-7 in Table I). To a solution of *tert*-butyl alcohol (0.74 g, 10 mmol) or an alkene (10 mmol) in acetic acid (2 ml) maintained at room temperature were successively added 95% sulfuric acid (50 mg, 0.027 ml) and a solution of α -oxo-benzeneacetonitrile (1.97 g, 15 mmol) in dichloromethane (4 ml). The reaction mixture was stirred for 6 h at room temperature whereupon dichloromethane (10 ml) and water (10 ml) were successively added. After the neutralization of aqueous phase of the resultant mixture with aqueous Na_2CO_3 solution, the mixture was stirred for 1 h at room temperature. The organic phase was isolated, and the aqueous phase was extracted with dichloromethane (8 ml). The organic phases were combined, washed with brine (10 ml) and dried over MgSO_4 . The solvent was evaporated and the crude product was subjected to column chromatography on silica gel using 10% ethyl acetate-hexane as the eluent.

The Ritter Addition of α -Oxo-benzeneacetonitrile to α -Trioxymethylene (Entry 2 in Table I). To 85% sulfuric acid (36 g, 20 ml) maintained at 0-5°C was added with stirring a mixture of α -oxo-benzeneacetonitrile (2.60 g, 19.8 mmol) and α -trioxymethylene (0.35 g, 3.89 mmol). The reaction mixture was stirred for 2 h at the same temperature, and poured into a large quantity of ice-cold water. After standing overnight the resultant precipitate was collected, and dissolved in appropriate amount of ether. The ether solution was repeatedly washed with aqueous Na_2CO_3 solution, dried over MgSO_4 . The solvent was evaporated and the crude product was recrystallized from 50% ethyl alcohol-hexane or benzene.

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